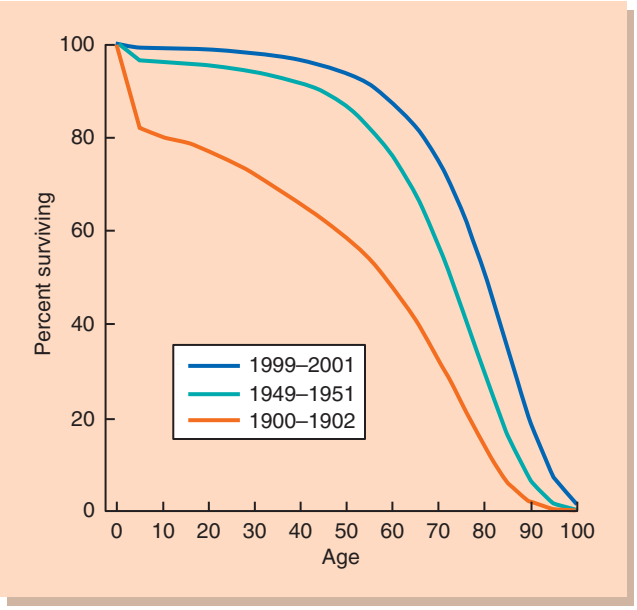

FIGURE 124-2 Percent surviving by age. Deaths tracked by state registries, 1900 to 1902, and by national registry, 1949 to 1951 and 1999 to 2001. (From Arias E, Curtin LR, Wei R, et al: U.S. decennial life tables for 1999-2001, United States life tables, Natl Vital Stat Rep 57:1–10, 2008.)

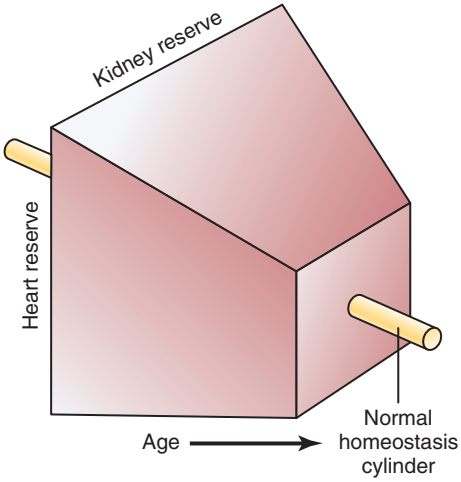

FIGURE 124-3 Classic schematic representation of decreased homeostatic reserve. (From Fries J, Crapo LM: Vitality and aging: implications of the rectangular curve, San Francisco, 1981, WH Freeman.)

survive to late life. Examination of survival curves across the twentieth century demonstrates a marked change in the shape of the overall graph from nearly linear in 1900 to rectangular in the 1990s, with much of the mortality compressed into late life (Fig. 124-2). Although the life expectancy at birth over the same period has risen dramatically from 47 years to nearly 77 years with up to 10% of the birth cohort surviving to age 95, the maximum lifespan defined as the age of the oldest surviving humans has remained remarkably stable.

THE BIOLOGY OF AGING

The relatively static nature of the maximum lifespan reflects the human body's limits at the cellular, tissue, and organ level in dealing with the stresses of aging. Across cell types and organ systems, certain consistent age-related alterations in function exist. Variability in tissue and organ function decreases, as evidenced by less fluctuation in heart rate or hormone secretion. Organ systems also exhibit predictable declines in function over time. These changes are most evident at times of stress, and ultimately these systems are slower to react and recover. The overall result is an impaired ability to deal with any demands beyond a narrow range outside the normal. This progressive restriction in the capacity to maintain homeostasis can be depicted as a steady tapering in the reserve available in multiple organ systems as time progresses (Fig. 124-3). In this situation an individual may function within the normal range in the absence of crisis, but stress such as acute illness may exceed his or her capacity to restore function and recover health. The result at best may be a decline in health and ability, and at worst, death.

THEORIES OF AGING

Scientific research provides a number of plausible theories of aging, which can be grouped into two major categories. *Error* or *damage theories* propose that aging occurs because of persistent threats from damaging agents and an ever-declining ability to respond to or repair this damage. *Program theories* postulate that genetic and developmental factors most significantly determine the biologic life course and the maximal age of the organism. In actuality, biologic aging may reflect a complex combination of many types of events.

The free radical theory of aging proposes that oxidative metabolism results in an excess of highly reactive byproducts, called *oxygen free radicals,* which damage proteins, DNA, and lipids. Molecular injury eventually leads to cell dysfunction and ultimately to tissue and organ disrepair. A second theory asserts that the accumulation of glucose-related molecules on proteins contributes to their dysfunction and degradation. These "glycosylated" molecules become more abundant over time and lead to impaired function at the tissue and organ level. Theory proponents point to the many chronic problems that routinely arise in patients with diabetes mellitus as proof of the significance of this phenomenon.

A different line of reasoning asserts that human lifespan and aging result from genetic-based timing mechanisms. Older theories suggest that evolutionary pressures are biased for traits that promote health and reproduction in early adulthood, possibly at the expense of health and function in late life. Furthermore, little selective pressure exists against negative traits that emerge in late life, leaving humans prone to the ill effects of aging. Geneticists have identified, among species of fruit flies and certain nematodes, specific genes that result in a significant prolongation in the organism's lifespan. Work is ongoing to discover similar genetic sequences among mammalian models.

Study of the enzyme telomerase has also generated much interest among theorists on aging. In a process called apoptosis, cells undergo programmed death to be replaced by younger cells. These divisions and replacements are limited by the number of generations intrinsic to a specific cell line (the Hayflick phenomenon). As telomeres located on the ends of chromosomes are depleted, cell aging and demise eventually occur. The enzyme telomerase prevents telomere shortening and may increase a cell's number of allotted replications and thereby extend the lifespan